

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/00, 31/165, 31/435, 31/46		A3	(11) International Publication Number: WO 94/01095 (43) International Publication Date: 20 January 1994 (20.01.94)
(21) International Application Number: PCT/GB93/01377 (22) International Filing Date: 30 June 1993 (30.06.93) (30) Priority data: 9214184.5 3 July 1992 (03.07.92) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): SANGER, Gareth, John [GB/GB]; BANNER, Stephen, Edward [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).			(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 14 April 1994 (14.04.94)
(54) Title: MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE			
(57) Abstract The invention relates to the use of those 5-HT ₃ receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT ₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.			

AL3

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LJ	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/01377

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/00 A 61 K 31/165 A 61 K 31/435 A 61 K 31/46														
II. FIELDS SEARCHED Minimum Documentation Searched ⁷ <table border="1"> <tr> <th>Classification System</th> <th>Classification Symbols</th> </tr> <tr> <td>Int.C1.5</td> <td>A 61 K</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			Classification System	Classification Symbols	Int.C1.5	A 61 K								
Classification System	Classification Symbols													
Int.C1.5	A 61 K													
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1"> <tr> <th>Category^o</th> <th>Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th>Relevant to Claim No.¹³</th> </tr> <tr> <td>X, D</td> <td>GUT vol. 31, no. 10 , 1990 page A1174 A. PRIOR ET AL. 'REDUCTION OF RECTAL SENSITIVITY AND POST-PRANDIAL MOTILITY BY GRANISETRON, A 5-HT3 RECEPTOR ANTAGONIST, IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)' cited in the application see abstract ---</td> <td>1-6,8</td> </tr> <tr> <td>A</td> <td>R.BERKOW, ED. 'THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, 15TH EDITION' 1987 , MERCK & CO. , RAHWAY, N.J. see page 808 - page 810 ---</td> <td>1-6,8</td> </tr> <tr> <td>X, P</td> <td>WO, A, 9211259 (BEECHAM GROUP PLC) 9 July 1992 see page 10, line 30 - line 31 see page 11, line 6 see page 13, line 31 - page 14, line 4 --- -/-</td> <td>1-6,8</td> </tr> </table>			Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X, D	GUT vol. 31, no. 10 , 1990 page A1174 A. PRIOR ET AL. 'REDUCTION OF RECTAL SENSITIVITY AND POST-PRANDIAL MOTILITY BY GRANISETRON, A 5-HT3 RECEPTOR ANTAGONIST, IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)' cited in the application see abstract ---	1-6,8	A	R.BERKOW, ED. 'THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, 15TH EDITION' 1987 , MERCK & CO. , RAHWAY, N.J. see page 808 - page 810 ---	1-6,8	X, P	WO, A, 9211259 (BEECHAM GROUP PLC) 9 July 1992 see page 10, line 30 - line 31 see page 11, line 6 see page 13, line 31 - page 14, line 4 --- -/-	1-6,8
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³												
X, D	GUT vol. 31, no. 10 , 1990 page A1174 A. PRIOR ET AL. 'REDUCTION OF RECTAL SENSITIVITY AND POST-PRANDIAL MOTILITY BY GRANISETRON, A 5-HT3 RECEPTOR ANTAGONIST, IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS)' cited in the application see abstract ---	1-6,8												
A	R.BERKOW, ED. 'THE MERCK MANUAL OF DIAGNOSIS AND THERAPY, 15TH EDITION' 1987 , MERCK & CO. , RAHWAY, N.J. see page 808 - page 810 ---	1-6,8												
X, P	WO, A, 9211259 (BEECHAM GROUP PLC) 9 July 1992 see page 10, line 30 - line 31 see page 11, line 6 see page 13, line 31 - page 14, line 4 --- -/-	1-6,8												
^o Special categories of cited documents : ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family														
IV. CERTIFICATION <table border="1"> <tr> <td>Date of the Actual Completion of the International Search 29-11-1993</td> <td>Date of Mailing of this International Search Report 18. 03. 94</td> </tr> <tr> <td>International Searching Authority EUROPEAN PATENT OFFICE</td> <td>Signature of Authorized Officer THEUNS</td> </tr> </table>			Date of the Actual Completion of the International Search 29-11-1993	Date of Mailing of this International Search Report 18. 03. 94	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer THEUNS								
Date of the Actual Completion of the International Search 29-11-1993	Date of Mailing of this International Search Report 18. 03. 94													
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer THEUNS													

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	WO,A,9214733 (SMITH-KLINE BEECHAM P.L.C.) 3 September 1992 see page 15, line 10 - line 11 see page 15, line 22 see page 18, line 8 - line 18 ---	1-6,8
X	EP,A,0289170 (BEECHAM GROUP PLC) 2 November 1988 see page 9, line 3 - line 4 see page 9, line 8 - line 9 see page 9, line 54 - page 10, line 1 ---	1-6,8
X,P	WO,A,9212149 (SMITH-KLINE BEECHAM PLC) 23 July 1992 see page 11, line 28 - line 29 see page 12, line 5 see page 14, line 29 - page 15, line 2 ---	1-6,8
X	ALIMENT.PHARMACOL.THER. vol. 6, no. 3, June 1992 pages 273 - 289 N.J.TALLEY 'REVIEW ARTICLE: 5-HYDROXYTRYPTAMINE AGONISTA AND ANTAGONISTS IN THE MODULATION OF GASTROINTESTINAL MOTILITY AND SENSATION: CLIMICAL IMPLICATIONS' see summary see page 278, last line - page 279, line 4 see page 280. clirical implications - page 282, first paragraph ---	1-6,8
X	EP,A,0387431 (BEECHAM GROUP PLC) 19 September 1990 see page 8, line 40 - line 41 see page 8, line 43 see page 9, line 33 - line 38 ---	1-6,8
X	WO,A,9205174 (BEECHAM GROUP PLC) 2 April 1992 see page 17, line 2 - line 3 see page 17, line 14 see page 20, line 5 - line 15 ---	1-6,8
X	WO,A,8909217 (BEECHAM GROUP PLC) 5 October 1989 see page 11, line 5 - line 6 see page 11, line 10 see page 14, line 1 - line 13 ---	1-6,8
X	WO,A,9101316 (BEECHAM GROUP PLC) 7 February 1991 see page 6, line 1 - line 2 see page 6, line 6 - line 7 see page 9, line 13 - line 23 ---	1-6,8
X,P	EP,A,0504679 (G.D.SEARLE & CO.) 23 September 1992 see page 4, line 58 see page 5, line 1 see page 36, line 23 - line 29 ---	1-6,8
	--- -/-	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0315316 (BEECHAM GROUP PLC) 10 May 1989 see page 8, line 40 see page 8, line 42 - line 43 see page 9, line 33 - line 38 ---	1-6,8
X	EP,A,0315390 (BEECHAM GROUP PLC) 10 May 1989 see page 9, line 48 - line 51 see page 10, line 44 - line 49 ---	1-6,8
X	EP,A,0287196 (BEECHAM GROUP PLC) 19 October 1988 see page 8, line 47 - line 51 see page 9, line 42 - line 47 ---	1-6,8
X,P	US,A,5137893 (G.D.SEARLE & CO.) 11 August 1992 see column 3, line 13 - line 14 see column 15, line 13 - line 19 ---	1-6,8
X	EP,A,0272876 (GLAXO GROUP LIMITED) 29 June 1988 see page 2, line 53 - line 54 ---	1-6,8
X	EP,A,0364274 (GLAXO GROUP LIMITED) 18 April 1990 see page 4, line 25 see page 5, line 37 - line 41 ---	1-6,8
X	EP,A,0381422 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 8 August 1990 see page 6, line 21 - line 22 see page 6, line 31 - line 34 ---	1-6,8
X	EP,A,0377967 (BEECHAM GROUP PLC) 18 July 1990 see page 8, line 5 - line 6 see page 8, line 11 see page 8, line 57 - page 9, line 4 ---	1-6,8
X	EP,A,0376624 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 4 July 1990 see page 4, line 53 - line 54 see page 5, line 55 - line 59 ---	1-6,8
X	EP,A,0189002 (SANDOZ AG) 30 July 1986 see page 19, line 17 see page 20, line 11 - line 22 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	US,A,5126343 (ZABROWSKI ET AL.) 30 June 1992 see column 11, paragraph 2 -paragraph 3 ---	1-6,8
X	WO,A,9107402 (PFIZER INC.) 30 May 1991 see page 1, line 12 - line 14 ---	1-6,8
X	EP,A,0317088 (GLAXO GROUP LIMITED) 24 May 1989 see page 5, line 44 see page 6, line 52 - line 57 ---	1-6,8
X	GB,A,2192885 (GLAXO GROUP LIMITED) 27 January 1988 see page 2, line 38 see page 3, line 36 - line 40 ---	1-6,8
X	EP,A,0357416 (GLAXO GROUP LIMITED) 7 March 1990 see page 3, line 1 ---	1-6,8
X	EP,A,0347229 (GLAXO GROUP LIMITED) 20 December 1989 see page 4, line 50 see page 5, line 51 - line 55 ---	1-6,8
X	EP,A,0356098 (GLAXO GROUP LIMITED) 28 February 1990 see page 5, line 5 see page 6, line 16 - line 20 ---	1-6,8
X	EP,A,0351385 (INSTITUTO DE ANGELI S.P.A.) 17 January 1990 see page 6, line 55 - line 56 ---	1-6,8
X	EP,A,0361317 (FUJISAWA PHARMACEUTICAL CO., LTD.) 4 April 1990 see page 13, line 29 - line 33 see page 12, line 4 see page 12, line 7 ---	1-6,8
X	EP,A,0358903 (DAINIPPON PHARMACEUTICAL CO., LTD.) 21 March 1990 see page 17, line 22 - line 39 ---	1-6,8
X	EP,A,0345956 (GLAXO GROUP LIMITED) 13 December 1989 see page 5, line 9 see page 6, line 18 - line 23 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X,P	EP,A,0518767 (MERRELL DOW PHARMACEUTICALS INC.) 16 December 1992 see page 2, line 4 see page 2, line 7 see page 11, line 27 - line 30 see page 14, line 26 - line 30 ---	1-6,8
X	EP,A,0454121 (G.D.SEARLE & CO.) 30 October 1991 see page 3, line 31 see page 3, line 34 ---	1-6,8
X	EP,A,0451538 (FUJISAWA PHARMACEUTICAL CO. LTD.) 16 October 1991 see page 14, line 22 see page 14, line 25 see page 14, line 41 - line 45 ---	1-6,8
X	EP,A,0419397 (A/S FERROSAN) 27 March 1991 see page 4, line 22 see claim 5 ---	1-6,8
X	EP,A,0417746 (G.D.SEARLE & CO.) 20 March 1991 see page 11, line 55 - line 56 see page 12, line 2 ---	1-6,8
X	EP,A,0385722 (GLAXO GROUP LIMITED) 5 September 1990 see page 4, line 44 see page 5, line 53 - line 58 ---	1-6,8
X	EP,A,0266899 (GLAXO GROUP LIMITED) 11 May 1988 see page 4, line 54 see page 5, line 54 - line 58 ---	1-6,8
X	EP,A,0254584 (BEECHAM GROUP PLC) 27 January 1988 see page 14, line 1 see page 14, line 13 see page 17, line 1 - line 13 ---	1-6,8
X	WO,A,9112254 (NOVO NORDISK A/S) 22 August 1991 see page 4, line 9 - line 11 see claim 5 ---	1-6,8
X	EP,A,0336759 (GLAXO GROUP LIMITED) 11 October 1989 see page 4, line 24 see page 5, line 25 - line 29 --- -/-	1-6,8

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
E	EP,A,0554794 (EISAI CO., LTD.) 11 August 1993 see page 30, line 50 - line 55 see page 31, line 7 - line 13 ---	1-6,8
X,D	EP,A,0450757 (GLAXO GROUP LIMITED) 9 October 1991 cited in the application see page 2, line 34 - line 35 see page 3, line 2 - line 3 ---	1-6,8
X	EP,A,0377967 (BEECHAM GROUP PLC) 18 July 1990 see page 8, line 4 - line 11 see page 8, line 57 - page 9, line 4 ---	1-6,8
X,D	EP,A,0279512 (BEECHAM GROUP PLC) 24 August 1988 cited in the application see the whole document -----	1-6,8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB93/01377

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see attached sheet ../..
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

For further information please see form PCT/ISA/206 sent to you 19.01.1994.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6 (partially), 8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

MEANINGFUL SEARCH NOT POSSIBLE OR INCOMPLETE SEARCH

1. The subject matter of claim 7 violates the requirements of Art. 6 and Rule 6.2 PCT. For that reason, no search was performed for the subject matter of claim 7.

2. In view of the definition of compounds by means of their pharmacological profile rather than by structural parameters, the search (within the framework of the first subject of the lack of unity objection) was limited to such compound(s) for which a structural identification was possible (Art. 6 PCT; Guidelines B-II, 7, last sentence, and B-III, 3.7).

3. The attention of the Applicant is drawn to the fact that the ISA is not in the position to perform experiments in order to identify known compounds having the presently claimed pharmacological utility as 5-HT₃ antagonists, or to assess the doses referred to in the claims. As a consequence it may very well be that relevant prior art has not been retrieved (Art. 6 PCT).

4. Although claims 1-2, 4-6 and 8-9 are directed to a method of treatment of the human/animal body (Rule 39.1(iv) PCT) the search for the first subject has been based on the alleged effects of the compound/composition.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9301377

SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9211259	09-07-92	AU-A- 9053391	22-07-92
		EP-A- 0563087	06-10-93
WO-A- 9214733	03-09-92	AU-A- 1209592	15-09-92
EP-A- 0289170	02-11-88	AU-A- 1510488	27-10-88
		DE-A- 3881950	29-07-93
		DE-T- 3881950	30-09-93
		JP-A- 63280061	17-11-88
		US-A- 4882327	21-11-89
WO-A- 9212149	23-07-92	AU-A- 1161292	17-08-92
		EP-A- 0566609	27-10-93
EP-A- 0387431	19-09-90	AU-B- 615991	17-10-91
		AU-A- 3132089	20-09-90
WO-A- 9205174	02-04-92	AU-A- 8624491	15-04-92
		CA-A- 2092431	27-03-92
		EP-A- 0550550	14-07-93
		PT-A- 99028	29-10-93
WO-A- 8909217	05-10-89	EP-A- 0363466	18-04-90
		US-A- 4871744	03-10-89
		US-A- 5049556	17-09-91
		US-A- 5200413	06-04-93
WO-A- 9101316	07-02-91	None	
EP-A- 0504679	23-09-92	US-A- 5260303	09-11-93
		AU-A- 1572892	06-10-92
		EP-A- 0530353	10-03-93
		JP-T- 6500124	06-01-94
		WO-A- 9215593	17-09-92
EP-A- 0315316	10-05-89	DE-A- 3868309	19-03-92
		JP-A- 1106867	24-04-89
		US-A- 4918079	17-04-90

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301377
SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0315390	10-05-89	JP-A- 1157978 US-A- 4959367	21-06-89 25-09-90
EP-A- 0287196	19-10-88	JP-A- 63222169 US-A- 4920127	16-09-88 24-04-90
US-A- 5137893	11-08-92	US-A- 5234921 US-A- 5227377 US-A- 5280029 US-A- 5219850 US-A- 5196547	10-08-93 13-07-93 18-01-94 15-06-93 23-03-93
EP-A- 0272876	29-06-88	AU-B- 618943 AU-A- 8261587 DE-D- 3787796 DE-T- 3787796 JP-A- 63246337	16-01-92 23-06-88 18-11-93 03-03-94 13-10-88
EP-A- 0364274	18-04-90	JP-A- 2209876 US-A- 5006544	21-08-90 09-04-91
EP-A- 0381422	08-08-90	AU-B- 626980 AU-A- 4889090 CN-A- 1045583 JP-A- 3223278 KR-B- 9311038	13-08-92 09-08-90 26-09-90 02-10-91 20-11-93
EP-A- 0377967	18-07-90	AU-B- 626614 AU-A- 4608189 JP-A- 2202890	06-08-92 21-06-90 10-08-90
EP-A- 0376624	04-07-90	AU-B- 630397 AU-A- 4714589 US-A- 4977175 JP-A- 3218362	29-10-92 28-06-90 11-12-90 25-09-91
EP-A- 0189002	30-07-86	DE-A- 3446484 DE-A- 3531281 DE-A- 3531282	03-07-86 12-03-87 12-03-87

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301377

SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0189002		AU-B- 595172	29-03-90
		AU-A- 5139685	31-07-86
		DE-A- 3587151	08-04-93
		JP-A- 2237920	20-09-90
		JP-B- 5088207	21-12-93
		JP-A- 61152628	11-07-86
US-A- 5126343	30-06-92	US-A- 4992461	12-02-91
		AU-A- 6231090	14-03-91
		CA-A- 2024964	12-03-91
		EP-A- 0417746	20-03-91
		JP-A- 3167189	19-07-91
WO-A- 9107402	30-05-91	CA-A- 2030077	18-05-91
		EP-A- 0434202	26-06-91
EP-A- 0317088	24-05-89	JP-A- 1258673	16-10-89
		US-A- 4939144	03-07-90
GB-A- 2192885	27-01-88	BE-A- 1000730	21-03-89
		CH-A- 674008	30-04-90
		DE-A- 3724322	28-01-88
		FR-A- 2601951	29-01-88
		JP-A- 63035570	16-02-88
		NL-A- 8701728	16-02-88
EP-A- 0357416	07-03-90	AU-B- 627768	03-09-92
		AU-A- 4096689	08-03-90
		JP-A- 2180823	13-07-90
EP-A- 0347229	20-12-89	JP-A- 2104585	17-04-90
		US-A- 5026722	25-06-91
EP-A- 0356098	28-02-90	AU-A- 2174288	09-03-89
		EP-A- 0306323	08-03-89
		JP-A- 2167280	27-06-90
		US-A- 5008272	16-04-91
EP-A- 0351385	17-01-90	AU-B- 622918	30-04-92

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301377
SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0351385		AU-A- 3803889	25-01-90
		JP-A- 2085253	26-03-90
		SU-A- 1776255	15-11-92
		US-A- 5047410	10-09-91
		US-A- 5252570	12-10-93

EP-A- 0361317	04-04-90	AU-B- 627221	20-08-92
		AU-A- 4140689	05-04-90
		JP-A- 2117675	02-05-90
		JP-B- 5004392	19-01-93
		US-A- 5173493	22-12-92

EP-A- 0358903	21-03-90	AU-B- 621642	19-03-92
		AU-A- 3910389	01-02-90
		JP-A- 5092959	16-04-93
		JP-A- 2256670	17-10-90
		US-A- 5017573	21-05-91
		US-A- 5166341	24-11-92

EP-A- 0345956	13-12-89	AU-B- 633254	28-01-93
		AU-A- 3499189	23-11-89
		JP-A- 2067280	07-03-90
		US-A- 4859662	22-08-89
		US-A- 5202343	13-04-93

EP-A- 0518767	16-12-92	EP-A- 0517984	16-12-92
		AU-A- 1803792	24-12-92
		JP-A- 5202044	10-08-93

EP-A- 0454121	30-10-91	US-A- 5140023	18-08-92
		AU-B- 630555	29-10-92
		AU-A- 7595191	07-11-91
		JP-A- 4225979	14-08-92
		US-A- 5223613	29-06-93

EP-A- 0451538	16-10-91	US-A- 5173493	22-12-92
		JP-A- 4270280	25-09-92

EP-A- 0419397	27-03-91	AU-B- 639487	29-07-93

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301377
SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0419397		AU-A- 6341490	08-04-91
		CA-A- 2066696	09-03-91
		WO-A- 9103475	21-03-91
		EP-A- 0491770	01-07-92
		JP-T- 5505171	05-08-93
EP-A- 0417746	20-03-91	US-A- 4992461	12-02-91
		AU-A- 6231090	14-03-91
		CA-A- 2024964	12-03-91
		JP-A- 3167189	19-07-91
		US-A- 5126343	30-06-92
EP-A- 0385722	05-09-90	JP-A- 3200786	02-09-91
		US-A- 5013733	07-05-91
EP-A- 0266899	11-05-88	JP-A- 63146874	18-06-88
		US-A- 4814344	21-03-89
EP-A- 0254584	27-01-88	DE-A- 3782107	12-11-92
		JP-A- 63039877	20-02-88
		US-A- 4822795	18-04-89
WO-A- 9112254	22-08-91	AU-A- 7340991	03-09-91
		EP-A- 0515537	02-12-92
		JP-T- 5504358	08-07-93
		US-A- 5187164	16-02-93
EP-A- 0336759	11-10-89	JP-A- 2049772	20-02-90
		US-A- 5116984	26-05-92
EP-A- 0554794	11-08-93	AU-A- 3217693	05-08-93
		CA-A- 2088702	05-08-93
		CN-A- 1075145	11-08-93
EP-A- 0450757	09-10-91	US-A- 5225407	06-07-93
EP-A- 0377967	18-07-90	AU-B- 626614	06-08-92
		AU-A- 4608189	21-06-90
		JP-A- 2202890	10-08-90

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301377

SA 76526

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/03/94.
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0279512	24-08-88	AU-B- 608276	28-03-91
		AU-A- 1035588	21-07-88
		JP-A- 63215627	08-09-88
		US-A- 4845092	04-07-89
		US-A- 4942160	17-07-90
		US-A- 5063231	05-11-91

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/00	A2	(11) International Publication Number: WO 94/01095 (43) International Publication Date: 20 January 1994 (20.01.94)
(21) International Application Number: PCT/GB93/01377 (22) International Filing Date: 30 June 1993 (30.06.93) (30) Priority data: 9214184.5 3 July 1992 (03.07.92) GB (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): SANGER, Gareth, John [GB/GB]; BANNER, Stephen, Edward [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		(74) Agent: JONES, Pauline; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.
(54) Title: MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE (57) Abstract <p>The invention relates to the use of those 5-HT₃ receptor antagonists, which are active in the Rat Model of Colo-rectal Distension at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also migraine.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

MEDICAMENTS FOR THE TREATMENT OF VISCERAL PAIN AND MIGRAINE

5 This invention relates to the use of certain compounds which are 5-HT₃ receptor antagonists as visceral analgesics.

EP-A-279512 (Beecham Group p.l.c.) describes the use of certain 5-HT₃ receptor antagonists, including granisetron (KYTRIL) in the treatment of visceral pain.

10 Visceral pain is a symptom of irritable bowel syndrome (IBS) and granisetron has been found to desensitise the rectum in IBS patients as shown by double-blind placebo-controlled studies, at doses of 120 µg/kg and 50 µg/kg, 120 µg/kg being most effective. (Prior and Read, 1990; Gut 31 (10) A1174).

15 Granisetron has been found to be active in an animal model of rectal sensitivity to distension (see method described hereafter).

5-HT₃ receptor antagonists which have the same effect as granisetron in this model, include zatosetron (Lilly) and metoclopramide.

20

The invention therefore relates to the use of those 5-HT₃ receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain, such as the pain symptoms of IBS, and also

25 migraine.

Preferred compounds are active at a lower dose than the 5-HT₃ receptor antagonist dose. Compounds which are approved or under clinical investigation are active at a similar dosage level to that which is used for antiemetic use.

30

Suitable modes of administration, formulations, etc. are as described in EP-A-279512.

5-HT₃ receptor antagonists which should be considered for this invention include

35 those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).

Rat Model of Colo-rectal Distension

- A 6-7 cm latex balloon was inserted intra-anally into male Wistar rats (250-650g) under halothane anaesthesia; the balloon catheter was taped to the tail. After recovery the animals were allowed unrestricted movement and were dosed with either vehicle (saline) or 5-hydroxytryptophan (5-HTP 10mgkg⁻¹ subcutaneously). At 5 min post-dose a ramp inflation of the colo-rectal balloon was carried out for approximately 10-30s until the visceromotor threshold (abdominal muscle contraction) was observed; the stimulus was then immediately removed and threshold pressure noted. This inflation procedure was repeated at 5 min intervals. 5-HT₃ receptor antagonists or saline were dosed subcutaneously after 3 stable responses were achieved and within 45 min of dosing 5-HTP or vehicle. The visceromotor threshold values were then recorded for a further 30 min. A similar model was described by Ness & Gebhart (1988, Brain Res. 450, 153-169). Maximum percentage changes (within the 30 min post-dose period) in distension pressure were compared with the mean of the pre-dose recordings. Saline control values were then assigned the value of 1.00 and drug induced changes compared directly.
- Saline vehicle had no effect on the visceromotor threshold, whilst the dose of 5-HTP caused a reduction in the distension pressure required to elicit a response to the noxious stimulus (mean reduction of $30.7 \pm 4.4\%$). Thus, by using a dose of 5-HTP that did not cause dramatic increases in gut secretion, the rat colo-rectum could be sensitised to colo-rectal distension.
- Addition of saline after a pre-dose of 5-HTP had no effect on the decrease in threshold pressure caused by 5-HTP. By comparison, it was found that some, BUT NOT ALL, 5-HT₃ receptor antagonists when administered after 5-HTP dose dependently raised the visceromotor threshold above pre-dose values, thereby displaying a reduction in the sensitivity of the sensitized colo-rectum and producing analgesia to noxious levels of visceral distension. The Table shows the differences between selected 5-HT₃ receptor antagonists. Note that those antagonists that are active as visceral analgesics all display bell-shaped dose effect curves.

-3-

COMPOUND	DOSE	INDEX	SEM
	$\mu\text{g/kg}^{-1}$		
saline	-	1.00	0.27
5-HTP	10 000	-1.63	0.23
granisetron	1	2.17	0.40
	10	4.18	0.59
	100	2.86	0.66
	1000	2.17	0.37
	10 000	2.00	0.69
tropisetron	10	1.31	0.33
	100	1.77	0.73
metoclopramide	1	1.88	0.35
	10	2.69	0.43
	100	2.15	0.65
BRL 46470	1	0.46	0.38
	10	1.50	0.32
	100	0.02	0.28
	1000	0.55	0.39
E5*	1	2.54	0.87
	10	4.31	0.60
	100	1.79	0.56
ondansetron	10	1.03	0.15
	100	0.94	0.20
	1000	0.44	0.24
	10 000	1.61	0.49
zatsetron	1	2.73	0.77
	10	3.55	0.44
	100	2.66	0.55

*Example 5 of EP-A-377967

Thus it can be seen that granisetron, E5 and zatosetron are visceral analgesics (increasing threshold values above control by > 4-fold) falling within the invention.

5

Intrathecal administration of granisetron (100mg) also showed good analgesic activity suggesting that a site of action, of those 5-HT₃ receptor antagonists that are visceral analgesics, may be in the spinal cord. Furthermore, recent evidence from neonatally capsaicin treated rats, where there is c-fibre deafferentation, suggests the presence of

10

these 5-HT₃ receptors on primary afferent fibres or a role for these receptors in sensory processing mediated by capsaicin sensitive afferents.

Claims

1. A method for the treatment and/or prophylaxis of visceral pain, in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT₃ receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model.
2. The use of those 5-HT₃ receptor antagonists, which are active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, in the treatment of visceral pain.
3. A pharmaceutical composition for use in the treatment and/or prophylaxis of visceral pain, which comprises a 5-HT₃ receptor antagonist, which is active in the animal model at a dose determined as the dose at which 5-HT₃ receptor antagonist activity is observed in standard tests, such as the Bezold-Jarisch model, and a pharmaceutically acceptable carrier.
4. A method, use or composition according to claim 1, 2 or 3 wherein the compound is active at a lower dose than the 5-HT₃ receptor antagonist dose.
5. A method, use or composition according to claim 4 for the treatment of the pain symptoms of IBS.
6. A method, use or composition according to claim 5 for the treatment of also migraine.
7. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is selected from those specifically and generically disclosed and referenced in EP-A-450757 (Glaxo Group Limited).
8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is granisetron.
9. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT₃ receptor antagonist is zatsetron (Lilly) or metoclopramide.